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## REMARKS

Claims 1-5 remain present for examination. Applicants respond below to the specific rejections raised by the Examiner in the final Office Action mailed December 7, 2004 and the Advisory Action mailed June 3, 2005. For the reasons set forth below, Applicants respectfully traverse.

### **Rejection under 35 U.S.C. §101 – Utility**

The Examiner has maintained the rejection of the pending claims under 35 U.S.C. § 101 as lacking patentable utility. The Examiner alleges that the specification provides data showing a small increase in DNA copy number, about 2-fold, in some normal tissues and cancer, however, there is no evidence regarding whether or not PRO1327 mRNA or polypeptide levels are also increased in these cancers. The Examiner cites Pennica et al. in support of her position that there is often a lack of correlation between DNA amplification and increased peptide levels. The Examiner states that Haynes et al. showed that polypeptide levels cannot be accurately predicted from mRNA levels, and that Hu et al. found that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. The Examiner concludes that, given the small increase in DNA copy number of PRO1327, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels. Further research is required, such that the asserted utility is not yet in currently available form.

Applicants respectfully submit that the Examiner has misunderstood the data presented in the specification, and that the claimed antibodies have utility in the field of cancer diagnostics and therapeutics.

### **Utility – Legal Standard**

According to the Utility Examination Guidelines (“Utility Guidelines”), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted “specific, substantial, and credible utility” or a “well-established utility.”

Under the Utility Guidelines, a utility is “specific” when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

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The requirement of “substantial utility” defines a “real world” use, and derives from the Supreme Court’s holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that “The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility.” In explaining the “substantial utility” standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a ‘substantial’ utility.” (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that “Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.” Further, “[T]o violate § 101 the claimed device must be totally incapable of achieving a useful result” *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), citing *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: “If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that “to overcome the presumption of truth that an assertion of utility by the applicant enjoys” the PTO must establish that it is “more likely than not that one of ordinary skill in the art would doubt (i.e., “question”) the truth of the statement of utility.” M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was

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sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.** M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

*Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient*

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, “unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.” *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or “more likely than not” standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

[T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true “beyond a reasonable doubt.” **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence “that one of ordinary skill in the art would reasonably doubt the asserted utility.” *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

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In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

[T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be “*reasonably* indicative of the desired [pharmacological] response.” In other words, there must be a **sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior.” *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art “to a reasonable probability.” In addition, the evidence need not be direct, so long as there is a “sufficient correlation” between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

[I]n *vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there

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no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is “an invariable exact correlation” between gene expression and protein expression. Instead, Applicants’ position detailed below is that a measured differential expression of mRNA in cancer cells establishes a “significant probability” that the encoded polypeptide will also be differentially expressed in the same cancer cells based on “a reasonable correlation therebetween.”

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.** The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the PRO1327 polypeptide and its antibodies are useful as diagnostic tools for cancer.

### **Substantial Utility**

#### *The Data in Example 18 are Data Regarding Differential mRNA Levels, not Gene Amplification*

Applicants begin by clarifying that the data concerning the differential expression of the PRO1327 gene presented in Example 18 relate to gene expression, **not gene amplification**. The description of Example 18 makes clear that the results were obtained by quantitative PCR amplification of cDNA libraries. It is well known in the art that cDNA libraries are made from mRNA, and reflect the level of mRNA for a particular gene in the source tissue. Thus, Example 18 is reporting a measure of the *expression* of the PRO1327 gene, i.e. mRNA levels, not its *amplification*, i.e. the number of copies of PRO1327 in the genome.

The PTO cites Pennica *et al.* as demonstrating that “what is often seen is a *lack* of correlation between DNA amplification and increased peptide levels.” Office Action at 4 (emphasis in original). Applicants point out that whether or not gene amplification leads to increased gene expression is irrelevant to this particular application. Likewise, whether the differential mRNA expression of the PRO1327 gene reported in Example 18 is due to an

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increase or decrease in copy number, or alternatively due to an increase or decrease in transcription rates is simply not relevant. Applicants have provided reliable evidence that the PRO1327 mRNA is differentially expressed in certain tumors. Whether this differential expression is due to changes in gene copy number, transcription rates, a combination of the two, or some other known or unknown cellular mechanism is simply not relevant to Applicants' asserted utility.

Applicants submit that the evidence of record establishes a specific and substantial utility for the PRO1327 polypeptides and antibodies with regard to the diagnosis and treatment of cancer. The Examiner states that "it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO1270 [*sic*] in tumor samples as contrasted to normal tissue samples: Only gene amplification data were presented." Applicants respectfully point out that the Examiner is incorrect in her interpretation of the data provided in the specification. The data provided in Example 18 of the instant specification shows that cDNA encoding PRO1327 is more highly expressed in normal esophagus, stomach, lung, rectum, and skin as compared to tumors in these same tissue types. Because cDNA libraries are prepared by isolating mRNA from a particular tissue and converting it to the corresponding cDNA, the expression data in Example 18 reflect levels of mRNA in the tested tissue types. The differential expression of PRO1327 polypeptide-encoding mRNAs in esophagus, stomach, lung, rectum, and skin tumors relative to normal tissues of the same type render the mRNAs useful for diagnosing and treating tumors in these tissues. Accordingly, the Examiner's assertions of uncertainty in the art regarding whether gene amplification translates to increased protein levels are not relevant to whether the claimed polypeptides and antibodies have utility. The differential expression of PRO1327 mRNAs in esophagus, stomach, lung, rectum, and skin tumors relative to normal tissues of the same type gives the mRNAs utility in diagnosing and/or treating cancer. A correlation between mRNA levels and protein levels, as established below, is sufficient to confer a similar utility on the PRO1327 polypeptides and antibodies.

#### Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies have utility as diagnostic and therapeutic tools for cancer, particularly esophageal, stomach, lung, rectum and skin cancer. Applicants are not asserting that the claimed antibodies necessarily

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provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools, to assist in the diagnosis of certain cancers. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1327 polypeptide is expressed at least two-fold higher in normal esophagus, stomach, lung, rectum and skin tissue than in tumor tissue of these same types;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. a decrease, generally leads to a corresponding change in the level of the encoded protein, e.g. a decrease;

3. Given Applicants' evidence that the level of mRNA for the PRO1327 polypeptide is decreased in esophageal, stomach, lung, rectal and melanoma tumors compared to normal tissues of these same types, it is more likely than not that the PRO1327 polypeptide is expressed at decreased levels in esophageal, stomach, lung, rectal and melanoma tumors compared to normal tissues of these same types;

4. Antibodies to proteins which are differentially expressed in certain tumors are useful as diagnostic and therapeutic tools.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the reliability of the evidence reported in Example 18;

2. The PTO cites Pennica *et al.*, Hu *et al.*, and Haynes *et al.*, to support the position that gene amplification is not *necessarily* correlated to gene expression, that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, and that mRNA levels are not predictive of protein levels;

3. The PTO concludes that based on the cited literature, one of skill in the art would not assume that higher expression of mRNA would correlate with increased polypeptide levels. Therefore, further research needs to be done to determine if the increase or decrease in PRO1327 DNA supports a role for the peptide in cancerous tissue.

As detailed below, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.02 III B. First, the PTO has failed to offer any evidence to support its rejection of the data in Example 18

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and the Declaration of Chris Grimaldi in support of these data. Second, as discussed above and can be seen from Applicants' summary of their argument, Applicants submit that any lack of correlation between gene amplification and gene expression is not at issue in this application and therefore the Pennica *et al.* reference is not relevant. Third, Applicants submit that the Haynes *et al.* and Hu *et al.*, references are not contrary to Applicants' arguments, and therefore are not evidence to support the PTO's position. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability**, that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

*Applicants have established that the Gene Encoding the PRO1327 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue*

Applicants first address the PTO's argument that the evidence of differential expression of the gene encoding the PRO1327 polypeptide in esophageal, stomach, lung, rectal and melanoma tumors is insufficient. Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish that the PRO1327 gene is differentially expressed in certain tumors.

The gene expression data in the specification, Example 18, shows that the mRNA associated with protein PRO1327 was more highly expressed in normal esophagus, stomach, lung, rectum and skin tissue than in tumors in these same tissues. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. Identification of the differential expression of the PRO1327 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the molecule useful as a diagnostic tool for the determination of the presence or absence of tumor. Applicants have previously submitted a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).



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In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest “can be used to differentiate tumor from normal,” thus establishing their reliability. He explains that, “The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue.” (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, “If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor.”

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that “[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned.” PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as “opinions” without

an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

Applicant's again point out that the data in Example 18 are gene expression data, not gene amplification data. The specification and the first Grimaldi Declaration make clear that Example 18 used semi-quantitative PCR of cDNA libraries. Therefore, one of skill in the art would know that Example 18 is a measure of mRNA levels, and reflects differential PRO1327 gene expression, not gene amplification. As discussed above, the PTO cites Pennica *et al.* for support of the argument that gene amplification does not necessarily lead to increased gene expression. This reference is irrelevant to the instant application which reports differential gene expression, not gene amplification. Therefore, this reference does not support the PTO's challenge of the sufficiency of the Example 18 data, or the first Grimaldi Declaration.

The PTO also cites Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) for support for its assertion the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. The PTO states that Hu teaches that not all genes with increased expression in cancer have a known or published role in cancer.

In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. See Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role

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for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker.

Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as molecular markers of cancer.

Applicants submit that a lack of known role for PRO1327 in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO1327 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors.

The position of the PTO is inconsistent with the analogous standard for therapeutic utility of a compound that "the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. §2701.01 (emphasis in original). Here, the mere identification of altered expression in tumors is relevant to the diagnosis of tumors, and, therefore, provides an immediate benefit to the public.

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In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1327 cDNA between esophageal, stomach, lung, rectal and melanoma tumors compared to normal tissues of these same types. Therefore, it follows that expression levels of the PRO1327 gene can be used to distinguish esophageal, stomach, lung, rectal and melanoma tumors from normal esophageal, stomach, lung, rectal and skin tissue, respectively. The PTO has not offered any significant arguments or evidence to the contrary.

As Applicants explain below, it is more likely than not that the PRO1327 polypeptide can also be used to distinguish esophageal, stomach, lung, rectal and melanoma tumors from normal tissue of these same types. This provides utility for the claimed antibodies to the PRO1327 polypeptides.

*Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between mRNA Levels and the Level of Expression of the Encoded Protein*

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants’ evidence of differential expression of the mRNA for the PRO1327 polypeptide in esophageal, stomach, lung, rectal and melanoma tumors, it is more likely than not that the PRO1327 polypeptide is differentially expressed; and antibodies to proteins differentially expressed in certain tumors have utility as diagnostic and therapeutic tools.

In response to Applicants’ assertion, the PTO cites Haynes *et al.* for its argument that “polypeptide levels cannot be accurately predicted from mRNA levels....” Office Action at 4. For the reasons discussed below, the cited reference is not contrary to Applicants’ asserted utility.

Haynes *et al.* studied whether there is a correlation between the level of mRNA expression and the level of protein expression for 80 selected genes from yeast. The genes were selected because they constituted a relatively homogeneous group with respect to predicted half-life and expression level of the protein products. See Haynes at 1863. Haynes did not examine whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Instead, Haynes determined whether the steady-state transcript level correlated with the steady-state level of the corresponding protein based on an analysis of 80 different genes.

Haynes reported to have “found a general trend but no strong correlation between protein and transcript levels (Fig. 1).” *Id.* However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, presented herein as Exhibit 2 (Gygi *et al.*, Molecular and Cellular Biology, Mar. 1999, 1720-1730). Gygi states that “there was a general trend of increased protein levels resulting from increased mRNA levels,” with a correlation coefficient of 0.935, indicating a strong correlation. Gygi at 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. *Id.* Considering that Example 18 of the specification shows over-expression of PRO 1003 mRNA in normal stomach and skin and in lung tumor, Haynes and Gygi actually provide strong evidence in support of a general correlation between mRNA and protein levels.

The PTO focuses on the portion of Haynes where the authors reported that for some of the studied genes with equivalent mRNA levels, there were differences in corresponding protein expression, including some that varied by more than 50-fold. Similarly, Haynes reports that different proteins with similar expression levels were maintained by transcript levels that varied by as much as 40-fold. *Id.* Thus, Haynes showed that for one type of yeast, similar mRNA levels for *different* genes did not universally result in equivalent protein levels for the *different* gene products, and similar protein levels for *different* gene products did not universally result from equivalent mRNA levels for the *different* genes. These results are expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein. Not surprisingly, based on these results, Haynes concluded that protein levels cannot always be accurately predicted from the level of the corresponding mRNA transcript *when looking at the level of transcripts across different genes.*

Importantly, Haynes did not say that for a single gene, the level of mRNA transcript is not positively correlated with the level of protein expression. Applicants have asserted that increasing or decreasing the level of mRNA for the same gene leads to a increase or decrease for the corresponding protein. Haynes did not study this issue and says absolutely nothing about it. Therefore, Haynes is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the PTO’s position.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants have previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the

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declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants have also submitted a copy of the declaration of Paul Polakis, Ph.D., also an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3<sup>rd</sup> ed. 1994) (submitted herewith as Exhibit 1) and (4<sup>th</sup> ed. 2002) (submitted previously). Figure 9-2 of Exhibit 1 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 1 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 1 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of

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regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made.” Exhibit 1 at 453 (emphasis added). Thus, as established in Exhibit 1, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In the previously submitted excerpt from Alberts, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that “a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*” (emphasis added). Similarly, Figure 6-90 on page 364 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, “the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes” (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, “[f]or most genes transcriptional controls are paramount” (emphasis added).

Further support for Applicants’ position can be found in the Lewin textbook, Genes VI, submitted herewith as Exhibit 2. The reference states “having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription.” *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, previously submitted. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed “a high degree of correlation between PSCA protein and mRNA expression.” Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that “it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA.” Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that “PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor.”

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Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), previously submitted, states the following:

The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Taken together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts from several leading textbooks and references provided above all establish that the *generally accepted understanding in the art* is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Applicants submit that a lack of known role for PRO1327 in cancer does not prevent its use as a diagnostic tool for cancer. The fact that there is no known translocation or mutation of PRO1327, for example, is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO1327 is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (See the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies. (See, e.g., U.S. Patent No. 6,414,117, U.S. Patent No. 6,124,433, U.S. Patent No. 6,156,500, and U.S. Patent No. 6,562,343 attached hereto as Exhibits 3-6.)

Accordingly, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1327 mRNA is more highly expressed in normal esophagus, stomach, lung, rectum and skin tissue than in tumors in these same tissue types, the PRO1327 polypeptide will also be more highly



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expressed in normal esophagus, stomach, lung, rectum and skin tissue than in tumors in these same tissue types. This differential expression of the PRO1327 polypeptide makes antibodies to it useful as diagnostic and therapeutic tools for cancer.

*The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"*

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

[T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection is only sustained where the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.**" M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original,

bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading textbooks in the field, and is supported by several additional references and the declarations of skilled experts.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that antibodies to a polypeptide differentially expressed in certain tumors can be used as a diagnostic tool. Pennica *et al.* is irrelevant to the utility of the claimed antibodies as Example 18 reports gene expression data, not gene amplification data. Likewise, neither Hu *et al.* nor Haynes *et al.* supports the PTO's position or is contrary to Applicants' asserted utility. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is credible and sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed antibodies can be used as diagnostic and therapeutic tools for cancer, particularly esophageal, stomach, lung, rectal, and melanoma cancer.

### **Specific Utility**

#### *The Asserted Substantial Utilities are Specific to the Claimed Antibodies*

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies related to PRO1327. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1327 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene for the PRO1327 polypeptide is expressed at least two-fold higher in normal esophagus, stomach, lung, rectum and skin tissue than in tumor in these same tissue types. These data are strong evidence that the PRO1327 gene and polypeptide are associated with esophageal, stomach, lung, rectal and melanoma tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1327 gene and polypeptide with a specific disease. The asserted utility for antibodies to the PRO1327 polypeptide as a diagnostic tool for cancer,

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particularly esophageal, stomach, lung, rectal and melanoma tumor, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

### **Conclusion**

The PTO has asserted several arguments to support its conclusion that based on the cited literature, one of skill in the art would not assume that higher expression of mRNA would correlate with increased polypeptide levels: (1) the PTO has challenged the reliability of the evidence reported in Example 18; (2) the PTO cites Pennica *et al.* to support its position that gene amplification is not necessarily correlated to gene expression; and (3) the PTO cites Hu *et al.*, and Haynes *et al.*, to support its assertion that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, and that mRNA levels are not predictive of protein levels. The PTO states that further research needs to be done to determine if the increase or decrease in PRO1327 DNA supports a role for the peptide in cancerous tissue. Applicants have addressed each of these arguments in turn.

First, Applicants have provided a first Declaration of Chris Grimaldi stating that the gene expression data in Example 18 are real and significant. This declaration also indicates that given the relative difference of at least two-fold in expression levels, the disclosed nucleic acids and corresponding polypeptides and antibodies have utility as cancer diagnostic tools. Applicants have shown that Pennica *et al.* is irrelevant to the asserted utility, and that Hu *et al.* does not support the PTO's position, and is not contrary to Applicants' asserted utility. Thus, the PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration.

Second, Applicants have shown that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in protein levels. Haynes *et al.* does not address this issue, and is not contrary to Applicants' asserted utility. Thus, the PTO has not offered any substantial reason or evidence to question these declarations and supporting references.

Third, Applicants have shown that it is not necessary to know what role PRO1327 plays in cancer to use it as a diagnostic tool. The PTO's own guidelines recognize this fact, and numerous patents have issued which claim differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies.

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Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed antibodies because the PRO1327 gene and polypeptide are differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of antibodies.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a “reasonable” confirmation of a real world context of use. Applicants remind the PTO that:

A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies relating to PRO1327 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

#### **Rejection under 35 U.S.C. §112 – Enablement**

The PTO has maintained its rejection of Claims 1-5 under 35 U.S.C. § 112, first paragraph. The PTO states that since the claimed invention is not supported by either a specific asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Applicants believe that the evidence, declarations, references, and arguments discussed above make clear that Applicants have established that one of skill in the art would be convinced, to a reasonable probability, that it is more likely than not that PRO1327 proteins are underexpressed in esophagus, stomach, lung, rectum, and skin tumors relative to normal tissues

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of the same type, and therefore have utility as a diagnostic tool for detecting tumors. This would include the use of the PRO1327 polypeptides to create diagnostic and therapeutic antibodies. This use is disclosed in the application, and the techniques for the creation of antibodies are well known and routine in the art. Thus, at least one use of PRO1327 polypeptides and antibodies is adequately enabled, which is all that is required – “if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.” M.P.E.P. 2164.01(c). In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

The Examiner states that Applicants point to the results of the amplification assay which showed an approximate 2-fold amplification of the PRO1327 DNA in some cancers and some normal tissues. The Examiner believes that one skilled in the art would not assume that a small increase in gene copy number, would correlate with significantly increased mRNA or polypeptide levels. Applicants again point out to the Examiner that the data in Example 18 is not gene amplification data. Rather, the expression data in Example 18 reflect levels of mRNA in the tested tissue types. The differential expression of PRO1327 polypeptide-encoding mRNAs in tumor tissues relative to normal tissues of the same type render the mRNA useful for diagnosing and treating tumors, specifically, esophagus, stomach, lung, rectum, and melanoma tumors.

Applicants respectfully submit that the great weight of the evidence supports the utility and enablement of the claimed antibodies and polypeptides. Applicants have provided numerous examples demonstrating a general understanding in the art that protein levels are regulated primarily by regulating mRNA levels in the large majority of cases, including the statements in Alberts, a leading textbook in the field of molecular biology, and the declarations of Dr. Polakis and Dr. Grimaldi, both experts in the field of cancer biology with numerous years of experience. Of particular significance is the fact that these references have identified the general understanding in the field, as opposed to isolated examples. In addition, the experiments testified to by Dr. Polakis as well as those in Haynes show a correlation between mRNA and protein levels for a large number of different genes. These references are in addition to the numerous examples of particular genes shown by Applicants, including those in Example 18 of the specification, and in Zhigang, and Meric. Applicants respectfully submit that the totality of the above-cited evidence clearly establishes that those of skill in the art would believe that mRNA levels more likely than not correlate with protein levels. In light of the fact that

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Applicants need not show a *necessary* correlation between mRNA and protein levels, Applicants respectfully submit that they have rebutted any prima facie case of non-utility and non-enablement the Examiner may have established. In fact, the "more likely than not" standard would effectively be an "absolute certainty" standard if the Examiner's few instances of post-transcriptional regulation were found to establish the non-existence of a general correlation between mRNA and protein levels in light of the totality of evidence produced above by Applicants. Accordingly, Applicants request withdrawal of the rejection of the pending claims under 35 U.S.C. §112.

### **Continuity**

The Examiner states that since the claimed invention does not have utility, the provisional patent applications listed, although disclosing the same experimental assays as the instant specification, do not impart utility to the instant invention. Therefore, the filing date of May 3, 2002 is considered the priority date.

Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 USC § 371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 USC § 119 to US Provisional Application 60/100684 filed 9/17/1998.

Applicants submit that for the reasons stated above, the claimed antibodies have a credible, substantial, and specific utility. The sequence of SEQ ID NO:92 was first disclosed in US Provisional Application 60/100684 filed September 17, 1998 in Figure 2 and SEQ ID NO:2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution) were first disclosed in PCT Application PCT/US00/23328 filed August 24, 2000, on page 93, line 3, through page 96, line 35. Thus, Applicants submit they are entitled to a priority date of at least August 24, 2000, if not the earlier date of September 17, 1998.

### **CONCLUSION**

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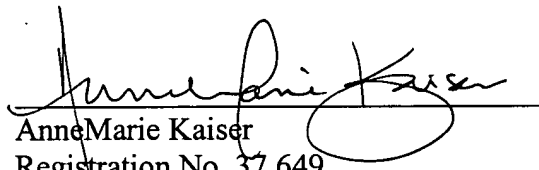
In view of the above, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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